

CLAIMS:

1. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases, comprising administering to the patient an effective amount of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide.

2. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases comprising the following steps:

(a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being clinically observable characteristics of a patient which deviate from the normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,

(b) administering to the patient a dose of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide,

(c) screening a panel of second messengers and signal transducers and selecting a repair marker, the intensity of which increases following administration of the therapeutic compound, where intensity is the extent to which the state of the repair marker differs from its state in the normal

condition, said repair marker being the concentration of a compound which participates in a cellular regulatory pathway which operates through protein kinase A, protein kinase C, or G-protein,

(d) administering the therapeutic compound at a dose level incrementally higher than the previous dose,

(e) repeating step (d) each time the intensity of the repair marker increases following an incrementally higher dose,

(f) repeating steps (d) and (e) until the intensity of the repair marker in step (c) no longer increases,

(g) continuing administration of the therapeutic compound at the highest dose level attained in step (f) until the intensity of the repair marker returns to the normal condition, and

(h) administering the therapeutic compound at a dose level incrementally higher than the previous dose and repeating steps (c), (d), (e), (f) and (g) with one or more additional repair markers until all disease markers of said set of disease markers no longer deviate from the normal condition.

3. The method of claim 2 further comprising:

(i) monitoring repair markers selected in steps (c) and (h) for 3 weeks following the last dose of the therapeutic compound given in step (h) and if the intensity of one or more repair markers deviate from the normal condition, reinitiating therapy in step (g) at the highest dose level achieved in step (h).

4. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases comprising the following steps:

- (a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being clinically observable characteristics of a patient which deviate from the normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,
- (b) administering to the patient a dose of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide,
- (c) screening a panel of second messengers and signal transducers and selecting a repair marker, the intensity of which increases following administration of the therapeutic compound, where intensity is the extent to which the state of the repair marker differs from its state in the normal condition, the repair marker being the concentration of a compound which participates in a cellular regulatory pathway which operates through protein kinase A, protein kinase C, or G-protein,
- (d) administering the therapeutic compound at a dose level incrementally higher than the previous dose,
- (e) repeating step (d) each time the intensity of the repair marker increases following an incrementally higher dose,

(f) repeating steps (d) and (e) until the intensity of the repair marker in step (c) no longer increases,

(g) administering the therapeutic compound at the dose level where the intensity of the repair marker no longer increases until the intensity of the repair marker returns to the normal condition,

(h) administering the therapeutic compound at a dose level incrementally higher than the previous dose and repeating steps (c), (d), (e), (f) and (g) with one or more additional repair markers until all disease markers of said set of disease markers no longer deviate from the normal condition, and

(i) administering the therapeutic compound at a dose level incrementally higher than the previous dose given in step (h) and repeating steps (c), (d), (e), (f) and (g) until the intensity of a universal marker returns to the normal condition, the universal marker being a constitutively expressed molecule which is transcriptionally activated by the therapeutic compound in all disease states.

5. The method of claim 4 further comprising:

(j) monitoring the universal marker for 3 weeks following the last dose given in step (i) and if the intensity deviates from the normal condition, reinitiating therapy at step (i) at the highest dose level achieved in step (i).

6. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases comprising the following steps:

(a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being clinically observable characteristics of a patient which deviate from the normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,

(b) administering to the patient a dose of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide, wherein the dose of the therapeutic compound is at a level which raises a universal marker to at least five times its normal level, the universal marker being a constitutively expressed molecule which is transcriptionally activated by the therapeutic compound in all disease states, and

(c) continuing to administer the therapeutic compound at the dose level of step (b) until the universal marker returns to its normal level.

7. The method of claim 6 wherein the universal marker is vWAg.

8. The method of claim 7 further comprising:

(d) monitoring the universal marker for 3 weeks following the last dose given in step (c) and if the intensity deviates from the normal condition, reinitiating therapy at step (c).

9. The method of claim 2, wherein the disease condition is HIV infection, wherein HIV is not expressed by said patient, and the concentration of at least one immunological molecule is elevated above the normal level comprising:

- a) administering to the patient an effective amount of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide, wherein the effective amount is the amount which causes a universal marker to rise at least five times its normal level, the universal marker being the concentration of a constitutively expressed molecule which is transcriptionally activated by the therapeutic compound in all disease states, and
- b) continuing to administer the effective amount of the therapeutic compound until the universal marker returns to its normal level.

10. The method of claim 9 wherein said immunological molecule is selected from the group consisting of CD4, CD25, IL-1, IL-3, IL-4, IL-6, TNF and sIL2R.

11. The method of claim 9 wherein the universal marker is the concentration of vWAg.

12. A method of treating a patient having a HIV associated disease state selected from the group consisting of tuberculosis, chronic wasting syndrome, and Herpesvirus infection comprising administering to an individual in need thereof an effective amount of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide.

13. A method of stimulating tissue repair associated with HIV infection comprising:

administering to a patient in need thereof, an effective amount of a therapeutic compound comprising a nucleic acid component of defibrotide, but not including defibrotide.

14. The method of claim 2 wherein the disease condition is HIV infection and wherein said disease marker is selected from the group consisting of odynophagia, arthralgia, Herpes labialis, Herpes genitalis, cryptosporidium diarrhea, Karnofsky performance score, waste syndrome, oral and pharyngeal candidiasis, and tuberculosis.

15. The method of claim 2 wherein said repair marker is selected from the group consisting of cAMP, cGMP, IL-1, IL-2, TNF- α , IL-6, cGMP/cAMP ratio, total lymphocyte count, T lymphocyte count, CD4 count, CD8 count, cAMP dependent protein kinase A enzyme, adenylate cyclase, G-protein, phosphoinositol, protein kinase C enzyme, inositol triphosphate, diacylglycerol, intracellular calcium level, intracellular calcium ion level, c-myc, ras, c-fos, c-jun, NK-kB, EIAI, AP-1, COUP, TCF-1 α , TATA, TAT element, oxygen radical, CREB, CREM, Platelet Derived Growth Factor (PDGF), Colony Stimulating Factor (CSF), Epidermal Growth Factor (EGF), Insulin Growth Factor (IGF), cytosolic tyrosine kinase, src, Src Homology 2 (SH2) domain, Src Homology 3 domain (SH3), serine/threonine kinase, Mitogen Activated Protein Kinase (MAP Kinase), Cytokine Receptor Superfamily, Signal Transducers and Activators of Transcription (STATs), JAJ1, JAK2, Tumor Necrosis Factor -Receptor 1 signal Transducer TRADD, chemokines of Rantes, and MIP-Alpha, and MIP-Beta.

16. The method of claim 1 wherein the nucleic acid component of defibrotide is an oligonucleotide from about 6 nucleotides to less than 60 nucleotides in length.

17. The method of claim 1 wherein the nucleic acid component of defibrotide is selected from the group consisting of dCTP, dATP, dGTP, dTTP, dAMP, dGMP, dCDP, dADP, ATP, AMP, CTP, CMP, UTP, cyclic TMP, cyclic UMP, cyclic GMP, GGTTGGATTGGTTGG (SEQ ID NO:1), GGTTGGATCGGTTGG (SEQ ID NO:2), GGATGGATCGGTTGG (SEQ ID NO:3) and GGTGGTGGTTGTGGT (SEQ ID NO:4).

18. The method of claim 1 wherein the nucleic acid component is a variant of an oligonucleotide selected from the group consisting of GGTTGGATTGGTTGG (SEQ ID NO:1), GGTTGGATCGGTTGG (SEQ ID NO:2), GGATGGATCGGTTGG (SEQ ID NO:3) and GGTGGTGGTTGTGGT (SEQ ID NO:4).

19. The method of claim 1 wherein the nucleic acid component is an oligonucleotide comprising the sequence of GGTGGTGGTTGTGGT (SEQ ID NO:4) and wherein said oligonucleotide is not a naturally existing nucleic acid component of defibrotide.

20. The method of claim 18, wherein the variant containing a sequence selected from the group consisting of HIV sequences, sequences encoding cellular regulatory factors and mitochondrial sequences.

21. The method of claim 20, wherein the variant is selected from the group consisting of GGGCTGTTGGCTCTGGTCTGCTCTGAAGGAAATCCCTGGCCTTCCCTTG (SEQ ID NO:15), ACCAGAGCCAACAGC (SEQ ID NO:16), and CCTGGCCTTCCCTTG (SEQ ID NO:17).

22. The method of claim 1 wherein the nucleic acid component is an oligonucleotide from about 25 nucleotides to about 30 nucleotides long and has a molecular weight of about 8171.58 Dalton.

23. The method of claim 1 wherein the nucleic acid component is an oligonucleotide from about 25 nucleotides to about 30 nucleotides long and has a molecular weight of about 8433.75 Dalton.

24. The method of claim 1 wherein the nucleic acid component of defibrotide is administered in combination with one or more sequence specific nucleic acid.

25. The method of claim 1 wherein the sequence specific nucleic acid is selected from the group consisting of

- an anti-protease sequence,
- a retroviral promoter sequence,
- a TAR sequence,
- a HIV mutant of TAR decoy RNA,
- a mutant TAR decoy RNA,
- a negative mutant of the viral REV transactivator,
- a synthetic promoter with the consensus sequence for binding of the transcription factor a Sp1 and the TATA box,
- a mutant of TATA box,
- a TAT mutant wherein the mutations involving the seven cysteine residues,

a sense, anti-sense, missense derivative of CIS acting negative elements (CRS) present in the integrase gene and REV mutant,

a transdominant suppressor of REV (mutations involving amino acid 78 and 79),

a NEF-cDNA sequence and its mutant with or without U3 region sequence of the 3'LTR,

a POL reverse transcriptase gene mutant,

a POL viral integrase gene and its mutant,

a POL viral protease gene mutant,

a HIV-I LTR enhancer (-137 to -17) mutant,

a HIV LTR promoter starting at -78,

a HIV LTR sequence encoding a arginine fork from aa27 to aa38,

a HIV-I LTR sense sequence of the negative regulatory element (-340 to -185),

a HIV-1 LTR consensus sequence for binding of transcription factors of AP1/COUP, NFAT-1, USF, TCF- α , NF-KB, TCF-1a, TBP, and an inhibitor of the consensus sequence,

a LTR NFkB mutant (-104 to -80),

a LTR Sp1 (GC box) binding site and TATA box mutant,

a LTR GAG gene sequence mutant,

a LTR mutant (-454 to +180),

a LTR genomic repeat at +80,

a LTR region responsive for cellular transcription factors between and to the left of U3 to -454 extending to -7,

a 3' LTR and its variant,

a 5' LTR and its variant,

a LTR variant,

an inhibitor of UBP-1 or LBP-1 binding sequence (-5 to +82),

a ENV, GAG, POL gene sequences placed 3' of the REV mutant codon,

a short sequence mutant (15-60 mer) and

a host DNA sequence of preferred targets for proviral integration.

26. The method of claim 1 wherein said nucleic acid component of defibrotide is a nucleic acid derivative.

27. The method of claim 1 wherein the dose of the therapeutic compound is from about 0.1 mg/kg patient body weight per day to about 1000 mg/kg patient body weight per day.

28. The method of claim 1 wherein the dose of the therapeutic compound is from about 40 mg/kg patient body weight per day to about 600 mg/kg patient body weight per day.

29. The method of claim 1 wherein the nucleic acid component of defibrotide is administered in combination with an amino acid selected from the group consisting of threonine, serine, tyrosine, and proline.

30. The method of claim 1 wherein the nucleic acid component of defibrotide is administered in combination with a N-containing ring compound

selected from the group consisting of pyrimidine, purine, adenylic acid, and guanosine.

31. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases, comprising administering to the patient an effective amount of a therapeutic compound comprising an oligonucleotide containing a homologous sequence of HIV and a gene encoding a cellular regulatory factor.

32. The method of claim 31 wherein the cellular regulatory factor is selected from the group consisting of human TNF receptor, mouse TNF-receptor CCCR5, human RIP protein kinase, IL-2 receptor, TNF receptor/cell death protein, IL-1 α , TNF- α , c-myc, c-abl, c-fos, c-ras, dystrophin, surface glycoprotein proteins of L-CAM and cathedrin, and B-myb.

33. The method of claim 32 wherein the oligonucleotide is selected from the group consisting of CAGCTGCACCTGCCAAGC (SEQ ID NO:5), ATAAAATATACCATATACA (SEQ ID NO:6), TCATAAAATATACTATATTCA (SEQ ID NO:7), ATATTAAAGAACGCTGTTTACAATACTTGG (SEQ ID NO:8), ATGCAGTTGTGAAGAGAA (SEQ ID NO:9), AATTAAGGCATAAGAAAATAAGAAATATGCAC (SEQ ID NO:10), TCTCTCCCTCAAGGACTCAGCTTTCTGAAG (SEQ ID NO:11), CAATAATAAAAGGGGAAA (SEQ ID NO:12), AGTGCAACCGGCAGGAGGTGA (SEQ ID NO:13), and

GCCACCAGCCCCTCCCCAGACTCTCAGGTGGAGGCAACAG (SEQ ID NO:14).

34. The method of claim 31 wherein the oligonucleotide is administered in combination with a homologous sequence of a gene encoding a cellular regulatory factor and GGTGGTGGTTGTGGT (SEQ ID NO:4).

35. The method of claim 34 wherein the cellular regulatory factor is selected from the group consisting of myc, TNF receptor, ras, abl, bcl, fos, IL-1, and musnos.

36. An oligonucleotide consisting of a sequence selected from the group consisting of CAGCTGCACCTGCCAAGC (SEQ ID NO:5), ATAAAATATACCATATACA (SEQ ID NO:6), TCATAAAATATACTATATTCA (SEQ ID NO:7), ATATTAAAGAACGCTGTTTACAATACTTGG (SEQ ID NO:8), ATGCAGTTGTGAAGAGAA (SEQ ID NO:9), AATTAAGGCATAAGAAAATAAGAAATATGCAC (SEQ ID NO:10), TCTCTCCCTCAAGGACTCAGCTTTCTGAAG (SEQ ID NO:11), CAATAATAAAAGGGGAAA (SEQ ID NO:12), AGTGCAACCGGCAGGAGGTGA (SEQ ID NO:13), GCCACCAGCCCCTCCCCAGACTCTCAGGTGGAGGCAACAG (SEQ ID NO:14), GGGCTGTTGGCTCTGGTCTGCTCTGAAGGAAATTCCCTGGCCTTCCCTTG (SEQ ID NO:15), ACCAGAGCCAACAGC (SEQ ID NO:16), and CCTGGCCTTCCCTTG (SEQ ID NO:17).

37. An oligonucleotide comprising the same sequence of an oligonucleotide of defibrotide obtainable via passing defibrotide through a C8 HPLC column and eluting with 0.1% TFA in water, wherein the length of the oligonucleotide of defibrotide is from about 25 to about 30 nucleotides and the molecular weight is 8171.58 Dalton, and wherein the oligonucleotide is not a naturally existing nucleic acid component of defibrotide.
38. A vector comprising an origin of replication and a sequence of the oligonucleotide in claim 36.
39. The vector of claim 38 further comprising a sequence encoding an origin of replication of mitochondrion.
40. The vector of claim 39 wherein the sequence encoding an origin of replication of mitochondrion is from a human.
41. The vector of claim 40 wherein the sequence is selected from the group consisting of 5' end of mitochondrial 12S RNA containing sequences from nucleotide 72 to 1025 and mitochondrial DNA containing sequences from nucleotide 1 to 72.
42. The vector of claim 40 further comprising a promoter sequence selected from the group consisting of TAR promoter, HIV LTR promoter, and promoter of DNA polymerase.
43. The vector of claim 42 further comprising a sequence encoding DNA polymerase.
44. The method of claim 1,2,4,6, 12 or 13 wherein the therapeutic compound comprising the vector of claim 38.

45. The method of claim 44 wherein the therapeutic compound is administered in combination with DNA polymerase, protease inhibitor, or reverse transcriptase.

46. A method of treating a patient having a resistance to a drug comprising administering an effective amount of a nucleic acid component of defibrotide in combination with the drug.

47. The method of 46 wherein the drug is protease inhibitor.

48. The method of claim 1 wherein the disease condition is HIV infection.

49. An oligonucleotide comprising the same sequence of an oligonucleotide of defibrotide obtainable via passing defibrotide through a C8 HPLC column and eluting with 0.1% TFA in water, wherein the length of the oligonucleotide of defibrotide is from about 25 to about 30 nucleotides and the molecular weight is 8433.75 Dalton, and wherein the oligonucleotide is not a naturally existing nucleic acid component of defibrotide.

50. A method of treating a disease condition in a patient selected from the group consisting of infectious diseases, genetic diseases, degenerative diseases, DNA damage, neoplasia, and skin diseases, comprising administering to the patient an effective amount of defibrotide in combination with one or more sequence specific nucleic acid.

51. The method of claim 50 wherein defibrotide is administered in combination with one or more sequence specific nucleic acid and one or more sequence specific peptide.

52. The method of claim 51, wherein a nucleic acid component of defibrotide is administered in combination with one or more sequence specific nucleic acid and one or more sequence specific peptide.